REMARKS

Reconsideration of the present application is respectfully requested in view of the above Amendments and the following Remarks. Applicants hereby cancel claims 6, 8-10, and 28-33 without acquiescence to any rejection and without prejudice to continuing prosecution of the canceled subject matter in a related divisional, continuation, or continuation-in-part application. Claims 1-5, 7, 11-23, 27, 34, and 35 have been amended to point out with more particularity certain embodiments of Applicants' invention. No new matter has been added to the claims. Support for the amended claims may be found throughout the application, for example, at page 7, lines 23-26, page 12, lines 8-14; page 13, line 11 through page 14, lin3 12; page 15, lines 4-21; page 16, lines 13-24; page 18, lines 6-22; page 18, line 28 through page 19, line 18; page 20, lines 28-29; and page 27, lines 12-26. Therefore, claims 1-5, 7, 11-27, 34, and 35 are now pending.

As indicated in the above Amendments, particular paragraphs of the specification have been amended to include sequence identifiers for nucleotide sequences disclosed in the application and Sequence Listing. The specification has also been amended to change the verb tense from past to present in Example 7, specifically, at the paragraphs beginning at page 53, line 19; page 54, line 24; and page 55, line 4. This Example has been amended to indicate that the example describes the steps of protocols and procedures that may be performed. No new matter has been added to the application.

OBJECTION UNDER 37 C.F.R. §§ 1.821-1.825 (SEQUENCE RULES)

The Examiner asserts that the application does not comply with the Sequence Rules under 37 C.F.R. §§ 1.821-1.825. Specifically, the Examiner asserts that sequence identifiers must be inserted into the specification to identify a disclosed sequence.

Applicants have herewith submitted amendments to the specification to include the sequence identifiers for specific amino acid and nucleotide sequences disclosed in the application. Accordingly, Applicants have amended Tables 4-6 (pages 46-47, 47, and 47-48, respectively) and have amended the paragraph beginning on page 48, line 15 to include sequence identifiers for each sequence. Applicants therefore submit that the application satisfies the

sequence requirements under 37 C.F.R. §§ 1.821-1.825 and respectfully request that the objection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejects claims 1-8, 11-27, 32, 34, and 35 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite.

The Examiner rejects claims 2 and 4, asserting that the claims are duplicate claims. Even though Applicants strongly disagree that original claims 2 and 4 were duplicate claims, this rejection is moot in view of the amendments submitted herewith. Amended claim 2 is directed to a pharmaceutical composition comprising a liposome and at least one polypeptide that comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO : 2, and amended claim 4 is directed to a composition wherein the at least one polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2. Accordingly, Applicants submit that claims 2 and 4 meet the requirements for definiteness under 35 U.S.C. § 112, second paragraph.

The Examiner rejects claims 1-8 and 11-12, asserting that the phrase "a liposome associated with at least one polypeptide" is vague.

Applicants respectfully traverse this rejection and submit that when read in light of the specification, the meaning of the claim is clear and definite. The specification describes that a polypeptide associated with a liposome is at least partially embedded in the liposome membrane, or alternatively, may be bonded to a lipid fatty acid tail that is embedded in the membrane (*see, e.g.,* page 11, line 29 through page 12, line 2). Nevertheless, without acquiescence or prejudice and solely to expedite prosecution of the present application, claims 1, 7, and 11 have been amended to recite that the composition comprises "a liposome *formulated* with at least one polypeptide," wherein "formulated" is a conventional term in the art. In addition, the meaning of the phrase is also described in the application, which teaches in detail methods for incorporating the polypeptide as recited into liposome formulations (*see, e.g.,* page

20, line 28 through page 25, line 7; page 53, line 15 through page 56, line 23 (Example 7)). Accordingly, Applicants submit that the present claims meet the requirements for definiteness according to 35 U.S.C. § 112, second paragraph.

The Examiner rejects claims 3 and 4, asserting that terms "fragment," "analog," "derivative," and "epitope bearing portion" are unclear. The Examiner also rejects claim 6, asserting that the phrase "epitope bearing portion" is unclear.

Applicants note that original claim 4 did not and presently amended claim 4 does not recite any of the aforementioned terms. Applicants further submit that in view of the amendments submitted herewith, the basis for this rejection has been obviated. While Applicants disagree that the terms derivative, analog, and epitope bearing portion are indefinite in view of the description in the specification, (*see e.g.,* page 13, lines 11-29; page 15, lines 4-21), without acquiescence and prejudice, and solely to expedite prosecution of the present application, Applicants have amended the claims such that none of the currently pending claims recites the terms "analog," "derivative," or "epitope bearing portion."

With respect to the term "fragment," in a certain embodiment, as presently recited in amended claim 5, a pharmaceutical composition comprises a liposome associated with a polypeptide fragment wherein the polypeptide fragment comprises at least 15 contiguous amino acids of SEQ ID NO : 2. Furthermore, the composition comprising such a fragment is capable of inducing an immune response against *Neisseria* (*see, e.g.,* page 13, line 11 through page 14, line 12; page 17, lines 18-25). Applicants therefore submit that the term "fragment" is clear and definite within the meaning of 35 U.S.C. § 112, second paragraph.

The Examiner also rejects claims 7, 8, and 35, alleging that recitation of a percent homology in combination with "fragments thereof" is indefinite. The Examiner further asserts that the metes and bounds of claim 8 cannot be determined in the absence of a recitation of a function.

Applicants submit that in view of the Amendments submitted herewith without acquiescence or prejudice, which includes the cancellation of claim 8, the basis for this rejection

has been obviated. Amended claim 7 is presently directed to a pharmaceutical composition comprising, in pertinent part, a polypeptide that comprises the amino acid sequence set forth in SEQ ID NO:2 wherein the N-terminal methionine at residue 1 is deleted or comprising a polypeptide that comprises the amino acid sequence set forth in SEQ ID NO:2, wherein the secretory amino acid sequence is deleted, and wherein the composition is capable of inducing an immune response against *Neisseria* (*see, e.g.*, page 14, lines 5-12; page 18, line 28 through page 19, line 18; page 31, lines 27-31).

Amended claim 35 is directed, in pertinent part, to a pharmaceutical composition comprising a liposome formulated with a polypeptide fragment comprising at least 15 contiguous amino acids of SEQ ID NO:2, wherein the composition is capable of eliciting antibodies that bind to *N. meningitidis* of any one of serogroup A, B, and C. Accordingly, the meaning of the term "fragment" recited in the instant claims is definite and clear as required under 35 U.S.C. § 112, second paragraph.

The Examiner rejects claim 32, asserting that the claim recitation of "a pharmaceutical method according to claim 1" lacks antecedent basis for the phrase "a pharmaceutical composition according to claim 1."

Applicants submit that in view of the Amendments submitted herewith, which include cancellation of claim 32 without acquiescence or prejudice, the rejection of claim 32 is moot.

Applicants therefore submit that the pending claims particularly point out and distinctly claim embodiments of Applicants' invention, thus satisfying the requirements for definiteness under 35 U.S.C. § 112, second paragraph. Applicants respectfully request that these rejections be withdrawn.

REJECTION UNDER 35 U.S.C. § 101

The Examiner rejects claim 32, under 35 U.S.C. § 101, asserting that the claim is directed to non-statutory subject matter.

Applicants submit that in view of the amendments to the claims submitted herewith, which includes cancellation of claim 32 without acquiescence or prejudice, this rejection of the claim is moot.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejects the "instant claims" under 35 U.S.C. § 112, first paragraph, alleging that the claimed subject matter is not enabled by the specification (*see* Action, page 7). The Examiner has not indicated in the Action which claims stand rejected for lack of enablement but has directed comments toward claims directed to pharmaceutical compositions, polypeptides, vaccines, and methods. Applicants' remarks below address rejection of the presently pending claims that are directed to pharmaceutical compositions and methods for using these compositions.

Applicants respectfully traverse this rejection and submit that the specification enables a person skilled in the art to make and use, without undue experimentation, the claimed polypeptides and related compositions. The presently claimed subject matter relates to pharmaceutical compositions comprising a liposome formulated with at least one NspA polypeptide that comprises the amino acid sequence set forth in SEQ ID NO:2, or variants thereof (*e.g.*, a polypeptide at least 80%, 90%, or 95% identical to SEQ ID NO : 2) or fragments thereof (*e.g.*, at least 15 contiguous amino acids of SEQ ID NO:2), wherein the composition is capable of inducing an immune response against *Neisseria*; to related compositions; and to methods of using these compositions.

Applicants submit, contrary to the PTO's assertions, that in view of the abundant guidance and direction provided in the specification, the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a skilled artisan to make and use the claimed compositions comprising a Neisserial surface protein A (NspA) polypeptide, or variants and fragments thereof, and related methods readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The specification provides guidance, including working examples, to teach a person skilled in the art how to use compositions comprising a NspA polypeptide (*e.g.*, SEQ ID NO:2) (*see, e.g.*, page 3, lines 18-24 and

reference cited therein) that comprises an amino acid sequence at least 80%, 90%, or 95% identical to SEQ ID NO:2, including a polypeptide that comprises the amino acid sequence set forth in SEQ ID NO:2 from which the N-terminal methionine residue at position 1 is deleted or that comprises the amino acid sequence set forth in SEQ ID NO:2, from which the secretory sequence (or signal peptide sequence) has been deleted. By using computer algorithms well known in the art and disclosed in the specification, such as CLUSTAL or the BLAST algorithm, a person skilled in the art can determine whether an unknown polypeptide shares at least 80% or greater amino acid sequence identity with the NspA amino acid sequence disclosed in the present application (*e.g.*, SEQ ID NO:2).

Furthermore, the specification teaches in great detail, how to make and use various NspA variants that are capable of inducing an immune response against *Neisseria*, including *N. meningitidis*. The specification describes the predicted three-dimensional structure of NspA that illustrates that regions of the protein include a periplasmic turn, membrane embedded region, and surface exposed loops; the specification further describes the amino acid residues of SEQ ID NO:2 that comprise each region (*see, e.g.,* page 6, lines 13-23; page 35, lines 28 through page 37, line 2) (Example 1); and Figure 2). NspA mutants were generated according to methods described in the application and routinely practiced in the art (*see, e.g.,* page 43, line 5 through page 48, line 4 (Example 4)) to characterize further the regions and residues of an NspA polypeptide that were capable of inducing an immune response against *N. meningitidis*. The specification further explicitly teaches a skilled artisan how to make NspA variants that are used in the claimed compositions by describing which particular regions of the polypeptide bind specifically to antibodies that are bactericidal and by describing particular regions of the polypeptide that bind specifically to antibodies that are not bactericidal and therefore more amenable to modification (*see, e.g.,* page 48, line 5 through page 52, line 11 (Example 5)).

Given this description of the NspA polypeptide, variants and fragments thereof, in the specification, a person skilled in the art may readily make modifications (*e.g.,* substitutions) to residues that are not implicated in specific binding to bactericidal antibodies and thus may reasonably and rationally predict modifications not affecting the capability of an NspA polypeptide variant or fragment thereof to induce an immune response against *Neisseria*. For

example, two peptides, between residues 41-55 and between residues 141-150 of SEQ ID NO:2, bind specifically to an antibody that does not bind to the surface of intact meningococcal cells. These two peptide regions are embedded in the meningococcal outer membrane and are thus not accessible to a bactericidal antibody (*see, e.g.,* page 48, lines 15-26). By contrast, regions of NspA that bind to bactericidal antibodies and are thus less amenable to modification are located in Loops 2 (amino acids 67 to 79) and 3 (amino acids at positions 111-122) (*see, e.g.,* page 50, line 4 through page 52, line 11). Thus, the present application provides abundant guidance to a person skilled in the art to make and use the claimed compositions comprising a liposome formulated with the NspA polypeptide and variants and fragments thereof.

An NspA polypeptide variant that retains the capability to induce an immune response against a *Neisseria* strain may comprise a substituted residue(s) that exhibits similar physical or chemical properties such as degree of hydrophobicity, size, or charge and has a minimal effect on the secondary structure and hydropathic nature of the polypeptide and thus, has a minimal effect on the polypeptide's immunogenicity and capability to elicit an immune response in a host (*see, e.g.,* page 15, line 23 through page 16, line 7). Whether a substitution, deletion, or addition of an amino acid to the polypeptide of SEQ ID NO:2 affects the immunogenicity of the polypeptide can be determined, readily and without undue experimentation, by any one of numerous immunoassays described in the application and routinely practiced in the art (*see, e.g.,* page 38, line 19 through page 43, line 2 (Example 3); page 48, line 5 through page 52, line 11 (Example 5); page 57, line 20 through page 60, line 2 (Example 9); page 60, line 6 through page 62, line 13 (Example 10)).

Furthermore, given the disclosure in the present specification, a person skilled in the art can readily make a pharmaceutical composition comprising a liposome formulated with a NspA polypeptide, or a variant thereof, and can readily determine without undue experimentation whether the NspA polypeptide elicits a protective immune response, which correlates with the presence of bactericidal antibodies, by using methods routinely practiced in the art and described in the specification (*see, e.g.,* page 56, line 26 through page 57, line 17 (Example 8); page 57, line 20 through page 60, line 2 (Example 9); page 60, line 6 through page 62, line 13 (Example 10); page 62, line 15, through page 66, line 15 (Example 11)). Performing

immunizations and conventional immunoassays to determine whether a candidate NspA variant polypeptide has retained immunogenic activity would not amount to undue experimentation, but instead is merely a matter of permissible routine screening. (*See In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening.")).

Moreover, the law is well settled that to satisfy the enablement requirement, an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polypeptide variants may be made, Applicants are not required to list all operable embodiments of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Applicants respectfully disagree with the assertion by the Examiner that the presently claimed invention is not enabled in view of the state of the art at the time of filing of the present application. In the Office Action, the Examiner points to several publications, including Rudinger (*in Peptide Hormones*, ed. Parsons (University Park Press 1976)) to support the assertion that substitution of one amino acid for another is unpredictable and requires "painstaking experimental study." Applicant notes that Rudinger, published in 1976, more than twenty-five years prior to the filing date of the present application, hardly reflects the state of the polypeptide, antibody, or molecular biology art, or the level of skill of a person practicing such an art at the time of filing of the present application.

In the intervening years between the publication by Rudinger and the filing date of the present application, molecular biology methods and techniques, including mutagenesis methods, have been developed and improved, permitting a skilled artisan to introduce mutations into a polypeptide and to evaluate the effect of such mutations readily and without undue experimentation. Random mutagenesis techniques, such as alanine scanning mutagenesis, error

prone polymerase chain reaction mutagenesis, and oligonucleotide-directed mutagenesis, some of which generate tens of thousands of mutants, are well known and have been used extensively in the art (*see, e.g.,* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 3rd ed., Cold Spring Harbor Laboratory Press, NY (2001)). Even assuming *arguendo*, as the Examiner asserts, that it cannot be predicted which positions within a protein's sequence can tolerate a substitution, deletion, or insertion of an amino acid, persons skilled in the art can alleviate these difficulties by using independent assays for assessing folding of the protein of interest (*see, e.g.,* Sambrook et al., page 13.3). Such assays commonly include, for example, the ability of the protein to react with mono- or polyclonal antibodies that are specific for native or unfolded epitopes, the retention of catalytic or ligand-binding functions, the sensitivity or resistance of the mutant protein to digestion with proteases, and other functional assays that characterize a particular polypeptide (*see* Sambrook et al., page 13.3; *see also, e.g.,* specification at pages 39, line 31 through page 44, line 14). Sambrook et al. further teach that the functions of proteins can be mapped to specific structural domains, undesirable activities of enzymes can be eliminated, and their desirable catalytic and physical properties can be enhanced. "In short, oligonucleotide-mutagenesis has become the genetic engineer's alchemy." (Sambrook et al., page 13.4).

Thus, Applicants submit that the scope of the present claims is commensurate with the disclosure in the specification, satisfying the requirements for enablement under 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejects claims 3-8, 32, 34, and 35 under 35 U.S.C § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. The Examiner asserts that the specification does not describe a polypeptide comprising an amino acid sequence that is at least 70-95% identical to SEQ ID NO:2.

Applicants respectfully traverse this rejection and submit that, as disclosed in the specification and recited in the instant claims, the application reasonably conveys to a person skilled in the art that Applicants possessed the claimed invention at the time of filing. With

respect to claims 6, 8, and 32, Applicants submit that the rejection of these claims is rendered moot by the amendments submitted herewith, which include cancellation of claims 6, 8 and 32, without acquiescence or prejudice.

Applicants respectfully submit that the subject matter of the pending claims as amended herewith is adequately supported by the specification and submit that the disclosure provides sufficiently detailed, relevant, and identifying characteristics, both structural and functional, of the claimed compositions comprising a liposome formulated with an NspA polypeptide as recited. A person skilled in the art would therefore be able readily to identify the species encompassed by the claims, given the recited structural features of the NspA polypeptide, variants, and fragments, and the recited functional feature that a composition comprising such an NspA polypeptide has the capability to induce an immune response against *Neisseria*, including *N. meningitidis*.

The specification describes the amino acid sequence, SEQ ID NO:2, of a full-length NspaA polypeptide, which is the detailed, chemical formula that describes the structure of the polypeptide; the specification also describes the polynucleotide sequence (SEQ ID NO:1) that encodes the polypeptide (*see, e.g.,* page 3, lines 22-24; page 6, lines 9-11; page 7, lines 28-31; Figure 1; Sequence Listing). Also described are fragments of the NspA polypeptide and variants thereof (*see, e.g.,* page 13, line 11 through page 14, line 12; page 15, lines 4-21). The specification further describes the predicted three-dimensional structure of the NspA polypeptide (*see, e.g.,* page 35, line 29 through page 37, line 2 (Example 1); Figure 2).

The functional characteristic that correlates with the polypeptide structure as described in the specification and recited in the instant claims includes the capability of the polypeptides to elicit an immune response against *Neisseria* (*see, e.g.,* page 38, line 20 through page 43, line 2 (Example 3); page 60, line 6 through page 66, line 15 (Examples 10 and 11)). The polypeptides that are formulated with a liposome in the claimed compositions may comprise one or more additions, substitutions or deletions of an amino acid of SEQ ID NO:2 (*see, e.g.,* page 15, line 4 through page 16, line 11). An exemplary polypeptide that comprises an amino acid sequence at least 90% identical to SEQ ID NO:2 is a polypeptide that has a deletion of the amino acid residues that correspond to the secretory amino acid sequence or that has a deletion of the N-

terminal methionine residue at position 1 of SEQ ID NO:2 (*see, e.g.,* page 18, line 28 through page 19, line 18). Moreover, the specification describes in detail regions of the NspA polypeptide that are exposed on the extracellular surface of a Neisseria cell and also describes localization of NspA epitopes to which bactericidal antibodies specifically bind (*see, e.g.,* page 43, line 5 through page 52, line 11 (Examples 4 and 5)).

The specification need not provide the polypeptide sequence for each variant or fragment thereof because the claims "need not be described in *haec verba* to satisfy the description requirement." *In re Smith*, 458 F.2d 1389, 59 C.C.P.A. 1025, 173 U.S.P.Q. 679 (1972). The specification need not describe each of the claim limitations exactly, "but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that applicants invented [the subject matter], including those limitations." *In re Wertheim*, 541 F.2d 257, 262; 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). Applicants submit that the present specification describes compositions comprising a liposome and NspA polypeptide variants and fragments thereof with sufficient, relevant, identifying characteristics to convey to a person skilled in the art that Applicants possessed the claimed invention at the time the Application was filed.

Applicants therefore submit that the application complies with the written description requirements under 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection of claims 3-5, 7, 34, and 35 be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

The Examiner rejects claims 1-8, 11-27, 32, 34, and 35 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over Brodeur et al. (WO 96/29412) (Brodeur) in view of any one of Ward et al. (*Microbiol. Pathogenesis* 21:499-512 (1996)) (Ward); Idanpaan-Heikkila et al. (*Vaccine* 13:1501-508 (1995)) (Idanpaan-Heikkila); or Wright et al. (*Infect. Immun.* 70:4028-34 (2002)) (Wright). The Examiner also rejects claims 1-8, 13-27, 32, 34, and 35 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over any one of Cadieux et al. (*Infect. Immun.* 67:4955-59 (1999)) (Cadieux); Plante et al. (*Infect. Immun.* 67:2855-61 (1999)) (Plante); or Martin et al. (*J. Exp. Med.* 185:1173-83 (1997)) (Martin) in view of any one of Ward; Idanpaan-Heikkila; or Wright.

As an initial matter, Applicants submit that in view of the Amendments submitted herewith, which includes cancellation of claims 6, 8, and 32, the rejection of these claims is moot. Applicants respectfully traverse these grounds of rejection and submit that Brodeur and any one of Ward, Idanpaan-Heikkila, and Wright taken alone or in combination, fail to teach or suggest the subject matter of claims 1-5, 7, 11-27, 34, and 35. Applicants further submit that none of Cadieux, Plante, and Martin, alone or in combination with any one of Ward, Idanpaan-Heikkila, and Wright teach or suggest the subject matter of claims 1-5, 7, 13-27, 34, and 35. As noted above, Applicant's invention is, in pertinent part, directed to a pharmaceutical composition comprising a liposome formulated with at least one polypeptide that comprises an amino acid sequence at least 80% identical to the amino acid sequence set forth in SEQ ID NO : 2, wherein the composition is capable of inducing an immune response against *Neisseria*, and to related compositions and methods.

Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (The PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination (*see In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

Applicants submit that each of the cited documents, alone or in any combination, fails to teach or suggest each feature of the currently pending claims. As acknowledged by the Examiner, Brodeur does not teach or suggest a pharmaceutical composition comprising a NspA polypeptide (*e.g.*, SEQ ID NO:2), variants or fragments thereof, and a liposome. Similarly, the Examiner agrees that none of Cadieux, Plante, or Martin teaches or suggests a pharmaceutical composition comprising an NspA polypeptide and a liposome. Each of Ward, Idanpaan-

Heikkila, and Wright fails to teach or suggest that a liposome may be combined with the NspA outer membrane protein. Ward describes combining liposomes with the class 1 porin (the *porA* gene product) only if the porin is expressed as a fusion polypeptide; Idanpaan-Heikkila describe producing the class 1 porin in *Bacillus subtilis* and reconstituting the polypeptide with phosphatidylcholine; and Wright describes combining liposomes with the PorB outer membrane protein. However, none of Ward, Idanpaan-Heikkila, and Wright describes using an NspA polypeptide. Each of these cited documents is nothing more than a cumulative reference in the art that describes the use of liposomes with a bacterial antigen. Even assuming *arguendo* that the cited documents disclosed each feature of the pending claims, absent some teaching or suggestion or indication of the desirability to combine features of a claimed invention that are present in the cited art, establishing obviousness on the basis that separate features existed in the prior art is insufficient (*see Ruiz and Foundation Anchoring Systems, Inc. v. A.B. Chance Company*, 234 F.3d 654, 665 (Fed. Cir. 2000)).

Furthermore, the teachings of the references fail to indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. Each of Ward, Idanpaan-Heikkila, and Wright instead suggest that the success of combining the antigen respectively described therein with a liposome to prepare an immunogenic composition is dependent upon the particular antigen and liposome. Ward determined that the *porA* gene fragment (*i.e.*, class 1 porin) was successfully expressed as a recombinant polypeptide only when fused to a bacteriophage coat protein. In addition, the composition comprising a liposome and the class 1 outer membrane porin more effectively induced bactericidal antibodies when the liposome/porin composition was administered to rabbits in the absence of an additional adjuvant (*see* Ward, Figure 4; discussion, last full paragraph; *see also* Idanpaan-Heikkila). By contrast, addition of an adjuvant to a liposomal composition comprising the PorB outer membrane protein enhanced the immunogenicity of PorB (*see* Wright).

Wright teaches that the addition of adjuvant to a PorB-liposome composition is similar to that observed when a Neisseria Opc protein was combined with a liposome and contrasts this observation with data obtained using PorA. Wright points out that even though the

PorA and PorB share significant amino acid sequence homology and both are believed to adopt a β-barrel confirmation in the outer membrane, the two porins have significant differences that contribute to the differences in how each of the two outer membranes may be combined with a liposome composition or a liposome plus adjuvant composition to obtain an immunogenic composition that might be useful as a vaccine against meningococcus (*see, e.g.,* Wright, at page 4033, column 1, full paragraph). Totally absent from the teachings or discussion in any of Wright, Ward, or Idanpaan-Heikkila, is any speculation, much less suggestion or teaching, of how to obtain Applicants' claimed compositions comprising a liposome and the NspA polypeptide (or variant or fragment thereof).

Thus, even if a person having ordinary skill in the art could combine the teachings of the cited art to achieve all the features of Applicants' invention, the cited documents fail to indicate which of the combinations of liposomes and adjuvants may be combined with the polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, or fragments or variants thereof, such that a person having ordinary skill in the art would be motivated to obtain the compositions described and claimed in the present application with any reasonable expectation of success. At best, the PTO's assertion of nonobviousness relies on the illegitimate test that a person having ordinary skill in the art might find it "obvious to try" to obtain the claimed compositions using the disclosure of the cited documents. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("...[W]hether a particular combination might be "obvious to try" is not a legitimate test of patentability.").

Accordingly, a person having ordinary skill in the art would have had no motivation or reasonable expectation of success to achieve the claimed embodiments of Applicants' invention as set forth in claims 1-5, 7, 11-27, 34, and 35 by combining the teachings of Brodeur with any one of Wright, Ward, or Idanpaan-Heikkila or as set forth in claims 1-5, 7, 13-27, 34, and 35 by combining the teachings of any one of Cadieux, Plante, or Martin with any one of Wright, Ward, or Idanpaan-Heikkila. Thus, each of the cited documents, alone and together, fails to provide any teaching, suggestion, or motivation to combine or modify the teachings therein to obtain a pharmaceutical composition comprising a liposome and a NspA

polypeptide, or variant or fragment thereof, that induces an immune response against *Neisseria* or to obtain a method for treating or preventing a *Neisseria* infection using these compositions.

Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants therefore respectfully request that the rejection of the claims be withdrawn.

Applicants submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

Mae Joanne Rosok

Mae Joanne Rosok
Registration No. 48,903

MJR:asl

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

833640_1.DOC